Ketamine in the Treatment of Bronchospasm During Mechanical Ventilation

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The effect of ketamine on bronchospasm during mechanical ventilation was evaluated in a prospective, placebo-controlled, double-blind trial. Fourteen mechanically ventilated patients with bronchospasm were randomly allocated to either ketamine 1 mg/kg or saline placebo. In the ketamine-treated patients, Po_2 increased from 10.5 (±0.5) kPa to 16.4 (±2.7) kPa ($P < .05$), whereas Po_2 in the placebo-treated patients remained unchanged. The Pco_2 was constant in the ketamine group, although it increased from 5.6 (±0.9) kPa to 6.1 (±0.9) kPa in the placebo group ($P < .05$). The pulmonary stethoscopic bronchospasm improved immediately after the administration of ketamine, whereas the thoracic compliance remained unchanged. In conclusion, the ketamine-treated patients showed an improvement by stethoscopic examination, in Po_2 and in Pco_2, suggesting that ketamine might be useful in the treatment of bronchospasm during mechanical ventilation. However, further studies are required to decide whether ketamine should be considered the drug of choice in patients with severe bronchospasm during ventilator treatment. (Am J Emerg Med 1994; 12:417-420. Copyright © 1994 by W.B. Saunders Company)

Ketamine possesses several characteristics that may participate in the reduction of airway pressure. It has a relaxing effect on the bronchial muscles,[1] it antagonizes the contraction of guinea pig and human bronchial preparations induced by histamine,[2,3] and it increases the plasma concentration of catecholamines by blocking the neuron-amine pump and by blocking the inactivation of catecholamines.[4]

In a retrospective study, ketamine reduced asthmatic symptoms at the induction and during the maintenance of anesthesia when compared with fentanyl-droperidol or inhalational agents,[5] and in a controlled study in which children were anesthetized with ketamine, the static compliance of the respiratory system was significantly greater than that in children anesthetized with halothane.[6] In eight case reports describing 15 patients, the positive effect of ketamine on severe asthma has been reported,[7-15] but the effects of ketamine in the treatment of bronchospasm during mechanical ventilation has not yet been investigated in a prospective, controlled study.

The number of deaths from asthma is increasing despite considerable improvement in drug treatment and management plans,[16] thus emphasizing the need for further treatment in severe asthma. The aim of this study was to evaluate the effect of ketamine on bronchospasm during mechanical ventilation.

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MATERIALS AND METHODS

The project was approved by the local Health Authorities and Ethics Committee, and informed consent was obtained from all subjects (when possible) or from their relatives. The study was performed in accordance with the Helsinki Declaration.

Fourteen mechanically ventilated patients with bronchospasm defined as thoracic compliance less than 35 mL/cm H_2O and stethoscopic expiratory wheezing were studied. All patients were ventilated by a Servo 900 B or C ventilator (Siemens-Elema, Sweden). The compliance was calculated as tidal volume/peak inspiratory pressure or positive end expiratory pressure (PEEP). The levels of pulmonary stethoscopic bronchospasm were evaluated in all patients on a scale from 0 to 4. At the time of inclusion, the intrinsic PEEP was measured by occlusion of the exhalation part of the ventilator, while delaying the onset of the next ventilator breath, as described by Pepe et al.[17,18] All patients had values less than 7 cm H_2O, thereby allowing for the maintenance of the ventilator setting and exclusion of a significant effect on the calculations of compliance.

Before including the patients in the study, 70 μg/kg midazolam (Roche, Copenhagen, Denmark) were administered intravenously (IV) to minimize the possibility of psychotomimetic side effects of ketamine and to reduce the possibility of the bronchospasm being induced by insufficient sedation. If no changes in the bronchospasm occurred within 15 minutes, patients were randomly allocated to a prospective, placebo-controlled, double-blind trial to receive either ketamine 1 mg/kg (Parke-Davis, Frederiksberg, Denmark) or saline placebo IV. Arterial blood gases (measured on ABL-2, Radiometer, Copenhagen, Denmark), thoracic compliance, stethoscopic bronchospasm, arterial pressure, and heart rate were measured immediately before administration of ketamine or placebo (t_0) and at intervals during the 60-minute study period. The ventilator setting was kept constant from 15 minutes before the study period to t_{60}, and all patients were intubated tracheally, at least 60 minutes before inclusion. Data were computerized on the StatView statistical package (Abacus, Berkeley, CA) using analysis of variance and are presented as mean ± standard error of the mean (SEM). $P < .05$ was considered significant.

RESULTS

Both groups consisted of seven patients and were comparable according to weight and age (Table 1). The mode of ventilation was composed of relative high frequency, low volume, high Fio_2, relative short pause time, and long inspiratory time as shown in Table 2. The differences between groups in ventilator data were statistically insignificant.

At the time of inclusion, the Po_2/Fio_2 ratio was 18.4 ± 2.5 in the ketamine group and 14.2 ± 1.1 in the placebo group ($P > .3$). Injection of midazolam did not relieve the broncho-

TABLE 1. Patient Data

Treatment Group	Patient	Sex/ Age (yr)	Weight (kg)	Indication for Mechanical Ventilation	Previous Asthma	Thorax X-ray	Broncholytic Therapy (Dosage)	Sedative (Dosage)	Outcome
Ketamine									
	1	F/77	50	Postoperative respiratory insufficiency	—	Atelectasis fibrosis	albuterol (10 μg/min)	Pentobarbital (50 mg/h)	Discharged from ICU
	2	M/29	70	Acute severe asthma	+	Normal	albuterol (40 μg/min), theophylline (15 μg/min)	Midazolam (10 mg/h)	Discharged from ICU
	3	M/67	64	Postoperative respiratory insufficiency and asthma	+	Atelectasis	albuterol (40 μg/min), theophylline (12 μg/kg/min)	Midazolam (5 mg/h) morphine (10 mg/h)	Discharged from ICU
	4	F/63	72	Aspiration pneumonia	—	Double-sided pneumonia	None	Midazolam (7 mg/h)	Discharged from ICU
	5	M/62	80	Pneumonia, myocardial infarction	—	Atelectasis	None	Midazolam (10 mg/h)	Deceased
	6	M/42	100	Pneumonia, shock, immunosuppression after transplantation	—	Double-sided pneumonia	Terbutalin (10 μg/min)	Midazolam (10 mg/h)	Deceased
	7	F/59	60	ARDS, septic shock	+	Diffuse pulmonary infiltration	albuterol (20 μg/min)	Midazolam (10 mg/h)	Deceased
Placebo									
	1	M/41	65	Pneumonia, asthma, drug addiction	+	Double-sided infiltration	albuterol (20 μg/min)	Pentobarbital (150 mg/h)	Deceased
	2	M/25	60	Aspiration pneumonia convulsions, drug addiction	+	Double-sided infiltration	None	Midazolam (15 mg/h)	Deceased
	3	F/73	60	Multiple rib fractures	—	Fractures, no infiltration	None	Morphine (7 mg/h)	Discharged from ICU
	4	M/58	68	ARDS, septic shock	—	Double-sided infiltration	None	Midazolam (4 mg/h)	Discharged from ICU
	5	M/62	70	Pneumonia, septic shock, cholascos	—	One-sided infiltration	None	Morphine (5 mg/h)	Discharged from ICU
	6	F/59	60	ARDS, septic shock	+	Diffuse pulmonary infiltration	albuterol (15 μg/min)	Midazolam (5 mg/h)	Deceased
	7	M/65	70	Postoperative pneumonia, asthma	+	Double-sided infiltration	albuterol (20 μg/min)	Diazepam (5 mg/h) morphine (5 mg/h)	Discharged from ICU

ABBREVIATIONS: ARDS, adult respiratory distress syndrome; ICU, intensive care unit.

spasm in any of the 14 patients. In the ketamine-treated patients, the Po_2 increased from 10.5 cm kPa at t_0 to 16.4 kPa at t_{60} ($P < .01$), whereas the Po_2 in the placebo-treated patients remained unchanged. The Pco_2 increased from 5.6 to 6.1 kPa in the placebo group ($P < .05$), whereas it was constant in the ketamine group. Oxygen saturation, pH, standard bicarbonate, and base excess showed no statistically significant changes during the study period (Table 3). The mean level of pulmonary stethoscopic bronchospasm at t_0 was 2.3 in both treatment groups (Figure 1). The stethoscopic finding was immediately improved by the administration of ketamine from 2.3 ± 0.2 at t_0 to 1.4 ± 0.2 at t_5 ($P < .05$) and remained at that lower level throughout the study period, whereas no improvement was seen after the administration of the placebo.

The thoracic compliance was equal in the two groups at t_0 and remained unchanged during the study period (Figure 1). No difference between groups in mean arterial pressure or heart rate was found. No residual psychotomimetic side effects occurred. Because the study included only 14 patients, any calculations on changes in survival rate were meaningless.

TABLE 2. Ventilator Data

Treatment Group	Tidal Volume (mL/min)	Frequency (min^{-1})	Fio_2 (%)	PEEP (cm H_2O)	Pause (%)	Inspiratory Time (%)
Ketamine	496 ± 43	19.6 ± 2.1	0.57 ± 0.06	10.7 ± 1.7	8.6 ± 1.4	34.4 ± 4.2
Placebo	624 ± 70	16.9 ± 1.2	0.66 ± 0.06	10.7 ± 1.3	10.0 ± 0	28.4 ± 2.7

NOTE: All values are mean ± SEM.

TABLE 3. Arterial Blood-Gas Values Before (t_0) and After (t_{60}) Treatment

Treatment Group/Time	Po_2 (kPa)	Pco_2 (kPa)	pH ($-\log[H^+]$)	Standard Bicarbonate (mmol/L)	Base Excess (mmol/L)	Oxygen Saturation (%)
Ketamine, t_0	10.5 ± 0.5	5.1 ± 0.6	7.36 ± 3.51	21.7 ± 2.3	−3.3 ± 2.6	94 ± 2.5
Ketamine, t_{60}	16.4 ± 2.7*	5.1 ± 0.6	7.33 ± 3.57	21.5 ± 2.0	−3.2 ± 2.6	98 ± 0.6
Placebo, t_0	9.4 ± 0.4	5.6 ± 0.9	7.34 ± 2.99	20.9 ± 1.4	−4.5 ± 1.6	94 ± 0.5
Placebo, t_{60}	10.4 ± 0.7	6.1 ± 0.9*	7.34 ± 2.67	21.1 ± 1.3	−3.5 ± 1.4	94 ± 0.5

NOTE: All values are mean ± SEM.
* Significant at $P < .05$.

Three patients in the ketamine group had a history of asthma (patient no. 2, 3, and 7; Table 1).

Patient no. 2 had severe status asthmaticus refractory to maximal broncholytic therapy. After the administration of ketamine, his thoracic compliance improved from 13.6 to 15.8 mL/cm H_2O. No changes were seen in stethoscopic wheezing or Po_2, whereas Pco_2 increased from 6.9 to 8.1 kPa.

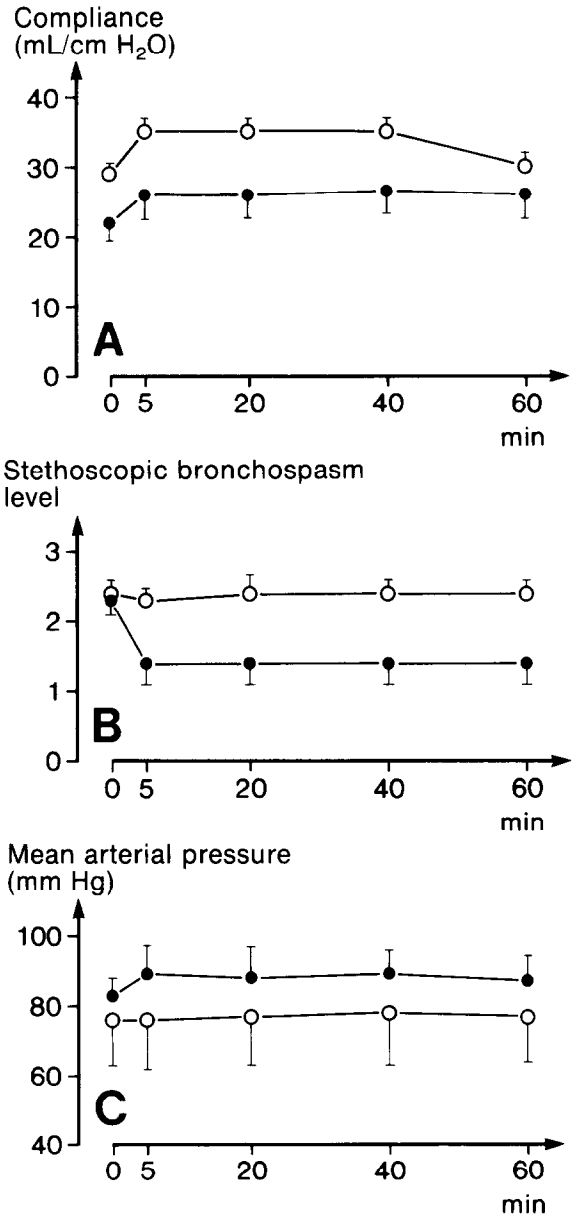

FIGURE 1. (A) Thoracic compliance (mL/cm H_2O), (B) stethoscopic bronchospasm level, and (C) mean arterial pressure (mm Hg) in the ketamine (●) and placebo-treated (○) groups. Mean ± SEM.

Patient no. 3 developed postoperative bronchospasm after abdominal aortic surgery and needed reintubation. After administration of ketamine the thoracic compliance improved from 26.0 to 32.5 mL/cm H_2O, the stethoscopic wheezing improved from 3 to 1, Po_2 increased from 8.7 to 10.2 kPa, and Pco_2 decreased from 7.8 to 6.4 kPa.

Patient no. 7 developed adult respiratory distress syndrome (ARDS) and bronchospasm due to a gram-negative sepsis. After ketamine administration an improvement in thoracic compliance from 23 to 25 mL/cm H_2O was seen, stethoscopic wheezing improved from 2 to 1, Po_2 increased from 11.8 to 23.0 kPa, and Pco_2 decreased from 5.5 to 5.2 kPa. Four patients in the placebo group had a history of asthma (patients no. 1, 2, 6, and 7; Table 1): Patients no. 1, 2, and 7 had double-sided pneumonia, and patient no. 6 had ARDS in relation to septic shock after intestinal perforation. No changes in thoracic compliance, stethoscopic finding, Po_2, or Pco_2 were seen during the study period.

DISCUSSION

In the present study, ketamine administration to patients with bronchospasm during ventilator treatment increased the Po_2 and may have prevented the increase in Pco_2 observed in the placebo-treated patients. In the ketamine group, a significant reduction in the stethoscopic expiratory wheezing occurred; however, this was not accompanied by an improvement in thoracic compliance.

Bronchospasm is a major hazard during mechanical ventilation because it may lead to hypoxia and hypercapnia through insufficient ventilation, and to barotraumas caused by increased inspiratory airway pressure. Bronchospasm may be caused by (1) irritation of the airway by the tracheal tube, hypersecretion, and suctioning; (2) disease in the pulmonary parenchyma, ie, pneumonia or stasis; or (3) asthma. These conditions all lead to ventilatory inhomogeneity.

The bronchospastic response to local irritation may be reduced by increasing the "depth" of the anesthesia. To reduce the possibility of the bronchospasm being induced by insufficient sedation, 70 μg/kg midazolam was administered IV in both groups before ketamine or placebo administration. This dose of midazolam does not cause the patient to be totally sedated or pain-free. Therefore, that the positive effect of ketamine in part may have been caused by its anesthetic activity cannot be excluded. On the other hand, it has been well established that benzodiazepines reduce the increase in circulating catecholamines that is usually caused

by ketamine.[4] Because catecholamines may be largely responsible for the broncholytic effect of ketamine, some of this broncholytic effect may have been reduced by the necessary administration of midazolam in the study design.

The effect of ketamine on a diseased pulmonary parenchyma is not known. Pulmonary hemodynamic responses to ketamine have been investigated in several studies, and an elevation in pulmonary arterial pressure and vascular resistance accompanied by an increase in total intrapulmonary shunt was found,[19,20] although these effects were not seen in children.[21] It is possible that these hemodynamic changes cause reduced perfusion through the hypoventilated areas and increased perfusion through normoventilated areas, thereby increasing the oxygen uptake.

The increase in cardiac output after ketamine administration and the subsequent positive inotropic effect on the left side of the heart may reduce a coexisting pulmonary edema, thereby improving pulmonary function and oxygen uptake.

The levels of pulmonary stethoscopic bronchospasm improved immediately after the administration of ketamine, whereas thoracic compliance remained unchanged. One explanation for this discrepancy may be that the pulmonary changes induced by ketamine are regional and, therefore, can be registered by the stethoscope, although the overall change in the pulmonary parenchyma is not sufficiently strong enough to cause a decrease in thoracic compliance.

Ketamine increases bronchial secretion, and it cannot be excluded that in some of our patients, the possible beneficial effect of ketamine was neutralized by increased secretion. However, this is unlikely to explain the discrepancy between wheezing and compliance.

Like many other investigations with critically ill patients, this investigation is complicated by the heterogeneity of the material. Better results may come from separating the different indications for artificial ventilation into different studies; ie, a study concerning status asthmaticus, a study for respiratory distress syndrome, and so forth.

In eight case reports describing 17 patients, the lifesaving effect of ketamine on severe asthma has been described.[7-15] In the present controlled study, the administration of ketamine increased Po_2, prevented the further deterioration of Pco_2, and caused a significant reduction in the stethoscopic expiratory wheezing; however, this was not accompanied by an improvement in thoracic compliance.

Further studies are required to decide whether ketamine should be considered as a last resort to prevent intubation and mechanical ventilation of patients with severe bronchospasm who are not responding to conventional therapy, and considered as a drug of choice in patients with severe bronchospasm during ventilator treatment.

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REFERENCES

1. Lundy PM, Gowdy CW, Colboun EH: Tracheal smooth muscle relaxant effect of ketamine. Br J Anaesth 1974;46:333-336

2. Wanna HT, Gergis SD: Procaine, lidokaine and ketamine inhibit histamine-induced contracture of guinea pig tracheal muscle in vitro. Anesth Analg 1978;57:25-27

3. Gateau O, Bourgain JL, Gaudy JH, et al: Effects of ketamine on isolated human bronchial preparations. Br J Anaesth 1989;63:692-695

4. Nedergaard OA: Cocaine-like effect of ketamine on vascular adrenergic neurons. Eur J Pharmacol 1973;23:153-161

5. Corssen G, Gutierrez J, Reves JG, et al: Ketamine in the anesthetic management of asthmatic patients. Anesth Analg 1972;51:588-594

6. Shulman DL, Bar-Yishay E, Gofrey S: Respiratory mechanics and intrinsic PEEP during ketamine and halothane anesthesia in young children. Anesth Analg 1988;67:656-662

7. Betts EK, Parkin CE: Use of ketamine in an asthmatic child. Anesth Analg 1971;81:588-590.

8. Fisher MM: Ketamine hydrochloride in severe bronchospasm. Anaesthesia 1977;32:771-772

9. Strube PJ, Hallam PL: Ketamine by continuous infusion in status asthmaticus. Anaesthesia 1986;41:1017-1019

10. Rock MJ, Rocha SRDL, L'Hommedieu CS, et al: Use of ketamine in asthmatic children to treat respiratory failure refractory to conventional therapy. Crit Care Med 1986;14:514-516

11. Park GR, Manara AR, Mendel L, et al: Ketamine infusion, its use as a sedative, inotrope and bronchodilator in the critically ill patient. Anaesthesia 1987;42:980-983

12. Boysen K, Strøm JJ, Eskildsen PC: Status asthmaticus treated with ketamine. Ugeskr Laeger 1987;149:2023-2024

13. L'Hommedieu CS, Arens JJ: The use of ketamine for the emergency intubation of patients with status asthmaticus. Ann Emerg Med 1987;16:568-571

14. Gram-Hansen P, Klausen NO: Ketamine in the treatment of severe therapy resistant status asthmaticus. Ugeskr Laeger 1987;150:492-493

15. Sarma VJ: Ketamine and asthma. Acta Anaesthesiol Scand 1992;36:106-107

16. Whitelaw WA: Asthma Deaths. Chest 1991;99:1507-1510

17. Pepe PE, Marini JJ: Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction. The auto-PEEP effect. Am Rev Respir Dis 1982;126:166-170

18. Miller RD (ed): Anesthesia, ed 3. New York, NY, Churchill Livingstone, 1990, pp 1152-1154

19. Tweed WA, Minuck M, Mymin D: Circulatory responses to ketamine anesthesia. Anesthesiology 1972;37:613-619

20. Gooding JM, Dimick AR, Tavakoli M, et al: A physiologic analysis of cardiopulmonary responses to ketamine anesthesia in noncardiac patients. Anesth Analg 1977;56:813-816

21. Hickey PR, Hansen DD, Cramolini GM, et al: Pulmonary and systemic hemodynamic response to ketamine in infants with normal and elevated pulmonary vascular resistance. Anesthesiology 1985;62:287-293